

REMARKS

Claims 49-52, 56-60 and 64 are pending and under examination. Claims 49 and 57 have been amended. Support for the amendments can be found throughout the specification and the claims as filed. In particular, support for the amendment to claims 49 and 57 to recite “stoichiometry of the reaction” can be found, for example, on page 8, third paragraph, to the paragraph bridging pages 8-9. Accordingly, these amendments do not raise an issue of new matter and entry thereof is respectfully requested. The Office Action mailed September 11, 2007, has been reviewed, and Applicant respectfully traverses all grounds of rejection for the reasons that follow.

Objection to the Claims

The objection to claim 57 for the informality of ending in two periods is respectfully traversed. Claim 57 has been amended to correct this inadvertent typographical error. Accordingly, Applicant submits that the objection has been rendered moot and requests that the objection be withdrawn.

Rejections Under 35 U.S.C. § 112, Second Paragraph

Claims 49-52, 56-60 and 64 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite. With respect to claim 49, the Examiner alleges that the phrase “determining substrates, products and stoichiometry for each of said metabolic genes” is unclear as to what set of quantities the stoichiometry is determined. Applicant respectfully submits that the meaning of this phrase would be clear to one skilled in the art. It is noted that this phrase was introduced when claim 49 was added in the response filed March 19, 2004, and was the subject of examination in the Office Actions dated June 18, 2004, May 4, 2005, February 22, 2006, December 22, 2006, and September 11, 2007, in which no issue was previously raised as to any alleged indefiniteness of this phrase, corroborating that this phrase is considered definite. Nevertheless, to further prosecution, claim 47 has been amended to recite “determining substrates, products and stoichiometry of the reaction for each of the gene products of said metabolic genes.” The specification teaches that the stoichiometry of each reaction provides the molecular ratios in which reactants are converted to products (page 8, third complete paragraph).

Accordingly, Applicant respectfully submits that this ground of rejection is moot and requests withdrawal of this rejection.

With respect to claim 57, the Examiner alleges that the phrase “determining substrates, products and stoichiometry for said metabolic gene product based on its assigned function” is unclear as to what basis the “function” has in determining stoichiometry between substrates, products and genes. It is noted that the phrase “based on its assigned function” was inadvertently retained when claim 57 was previously amended to delete the antecedent basis for this phrase. Accordingly, this phrase has been deleted from claim 57. The Examiner has additionally indicated that the phrase “said metabolic gene product” in lines 5-6 is unclear for insufficient antecedent basis. Claim 57, step b), has been amended to recite “the gene product of said metabolic gene” to correct antecedent basis. The Examiner has additionally asserted that claim 57 is unclear for the phrase “the metabolic genes product in said microbe” as to whether there are multiple genes having a single product. Claim 57 has been amended to recite “gene products” to correct the inadvertent typographical error. Accordingly, Applicant respectfully submits that this ground of rejection is moot and requests withdrawal of this rejection.

Rejections Under 35 U.S.C. § 103

Claims 49-52 and 56-60 stand rejected under 35 U.S.C. § 103 as allegedly obvious over Pramanik et al., Biotechnol. Bioengineer. 56:396-421 (1997), in view of Blattner et al., Science 277:1453-1469 (1997). The Examiner alleges that the study of Pramanik et al. investigates the stoichiometric model of *E. coli* metabolism and studies many metabolic reactions that take place within *E. coli*. The Examiner acknowledges that Pramanik et al. does not teach obtaining a plurality of DNA sequences comprising most of the metabolic genes in a genome, determining open reading frames of these genes, assigning functions to the proteins encoded by the open reading frames, and determining which of the open reading frames correspond to metabolic genes. The Examiner alleges that the study of Blattner et al. maps the complete genome sequence of *Escherichia coli* K-12. The Examiner asserts that it would have been obvious to modify the stoichiometric model of *E. coli* metabolism as described by Pramanik et al. by use of the complete genome sequence of Blattner et al., where the motivation would have been that by knowledge of the full genome of *E. coli*, not only can metabolism be further analyzed but also

knowledge of the entire sequence of *E. coli* enables global approaches to understanding biological function in living cells and has led to new ways of looking at the evolutionary history of bacteria (referring to first paragraph of introduction on page 1453 of Blattner et al.).

Applicant respectfully points out that both of these references have previously been cited, and the rejections over these references have been withdrawn. As stated in MPEP § 707.07(g), “[P]iecemeal examination should be avoided as much as possible. The examiner ordinarily should reject each claim on all valid grounds available, avoiding, however, undue multiplication of references.” Applicant respectfully submits that re-citing references that have already been addressed on the record and distinguished from the claims is not in the spirit of avoiding piecemeal examination.

With respect to the alleged obviousness over the cited references, to establish a *prima facie* case, the Office must satisfy three requirements. First, the prior art relied upon, coupled with the knowledge generally available in the art at the time of the invention, should contain some suggestion or incentive that would have motivated the skilled artisan to modify a reference or to combine references. See *Karsten Mfg. Corp. v. Cleveland Gulf Co.*, 242 F.3d 1376, 1385, 58 U.S.P.Q.2d 1286, 1293 (Fed. Cir. 2001); *C.R. Bard, Inc. v. M3 Sys., Inc.*, 157 F.3d 1340, 1352, 48 U.S.P.Q.2d 1225, 1232 (Fed. Cir. 1998); *Northern Telecom v. Datapoint Corp.*, 908 F.2d 931, 934, 15 U.S.P.Q.2d 1321, 1323 (Fed. Cir. 1990). Second, the proposed modification of the prior art must have had a reasonable expectation of success, determined from the vantage point of the skilled artisan at the time the invention was made. In other words, a hindsight analysis is not allowed. See *Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1209, 18 U.S.P.Q.2d 1016, 1023 (Fed. Cir. 1991); *In re Erlich*, 3 U.S.P.Q.2d 1011, 1016 (Bd. Pat. App. & Int. 1986). Lastly, the prior art reference or combination of references must teach or suggest all the limitations of the claims. See *In re Wilson*, 424 F.2d 1382, 1385, 165 U.S.P.Q. 494, 496 (C.C.P.A. 1970).

Applicants respectfully maintain that the Office has not met the burden the law allocates to it with regard to establishing a *prima facie* case of obviousness, which requires that the prior art references relied upon give rise to the requisite motivation to combine their content and, when viewed in combination, provide the skilled person with a reasonable expectation of success to

achieve the claimed invention, and, further that all the limitations of the claims must be taught or suggested.

Applicant respectfully submits that there is no suggestion or motivation to combine Pramanik et al. with Blattner et al. to produce the claimed methods for simulating a metabolic capability of an *in silico* strain of a microbe. In regard to Pramanik et al., this reference is cited allegedly for describing the production of a stoichiometric model of *E. coli* metabolism. However, as previously discussed on the record and as described in the subject application at, for example, page 4, first paragraph, Pramanik et al. teach away from using models that are not produced from existing biochemical information. Pramanik et al. is distinguished in the application where it describes:

In one example, Pramanik et al. described a stoichiometric model of *E. coli* metabolism using flux-balance modeling techniques (*Stoichiometric Model of Escherichia coli Metabolism: Incorporation of Growth-Rate Dependent Biomass Composition and Mechanistic Energy Requirements, Biotechnology and Bioengineering*, Vol. 56, No. 4, November 20, 1997). However, the analytical methods described by Pramanik, et al. can only be used for situations in which biochemical knowledge exists for the reactions occurring within an organism. Pramanik, et al. produced a metabolic model of metabolism for *E. coli* based on biochemical information rather than genomic data since the metabolic genes and related reactions for *E. coli* had already been well studied and characterized. Thus, this method is inapplicable to determining a metabolic model for organisms for which little or no biochemical information on metabolic enzymes and genes is known. It can be envisioned that in the future the only information may have regarding an emerging pathogen is its genomic sequence.

Application, page 4, first paragraph [emphasis added].

Accordingly, the cited combination of references fail to teach, suggest or provide a motivation to construct a stoichiometric matrix as claimed because Pramanik et al. teach away from generating a metabolic model absent actual knowledge of biochemical information. Moreover, Blattner et al. does not cure the deficiencies of Pramanik et al. In the Office Action, it appears to be suggested that the motivation to combine Pramanik et al. with Blattner et al. “would have been that by knowledge of the full genome of *E. coli*, not only can metabolism be further analyzed, but also knowledge of the entire sequence of *E. coli* enables global approaches to understanding biological function in living cells and has led to new ways of looking at the evolutionary history of bacteria [see first paragraph of introduction on page 1453].” The latter

part of this sentence is almost verbatim from the last sentence of the first paragraph of Blattner et al. Turning to this paragraph in Blattner et al., this passage is set forth in the following context:

Genome sequences, especially those of well-studied experimental organisms, help to integrate a vast resource of biological knowledge and serve as a guide for further experimentation. Availability of the complete set of genes also enables global approaches to biological function in living cells (4) and has led to new ways of looking at the evolutionary history of bacteria (5).

It is clear that this passage in Blattner et al. relates generally to the knowledge gained from having genome sequence information and its ability to serve as a guide for further experimentation. Such general statements about genome sequences enabling “global approaches to biological function in living cells” and providing “new ways of looking at the evolutionary history of bacteria” in no way provides motivation to combine Blattner et al. with Pramanik et al. or to modify Pramanik et al. to arrive at Applicant’s claimed methods.

As stated in MPEP § 2143 (G):

(G) Some Teaching, Suggestion, or Motivation in the Prior Art That Would Have Led One of Ordinary Skill To Modify the Prior Art Reference or To Combine Prior Art Reference Teachings To Arrive at the Claimed Invention

To reject a claim based on this rationale, Office personnel must resolve the Graham factual inquiries. Then, Office personnel must articulate the following:

- (1) a finding that there was some teaching, suggestion, or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings;
- (2) a finding that there was reasonable expectation of success; and
- (3) whatever additional findings based on the Graham factual inquiries may be necessary, in view of the facts of the case under consideration, to explain a conclusion of obviousness.

The rationale to support a conclusion that the claim would have been obvious is that “a person of ordinary skill in the art would have been motivated to combine the prior art to achieve the claimed invention and that there would have been a reasonable expectation of success.” *DyStar Textilfarben GmbH & Co. Deutschland KG v. C.H. Patrick Co.*, 464 F.3d 1356, 1360, 80 USPQ2d 1641, 1645 (Fed. Cir. 2006). If any of these findings cannot be made, then this rationale

cannot be used to support a conclusion that the claim would have been obvious to one of ordinary skill in the art. [emphasis added]

It is respectfully submitted that the rationale that there was motivation to modify or combine the cited references is not tenable in the present case. First, as discussed above, there was no motivation in either Pramanik et al. or Blattner et al. to combine these references. To the contrary, Pramanik et al. actually teaches away from generating a metabolic model absent actual knowledge of biochemical information. Also, the general statements in Blattner et al. of the knowledge gained from having genomic sequences in no way provides motivation to combine the description in Blattner et al. of the genome sequence of *E. coli* K-12 with Pramanik et al. Moreover, there would have been no reasonable expectation of success. To the contrary, as discussed in the specification, Pramanik et al. indicates that “the analytical methods described by Pramanik, et al. can only be used for situations in which biochemical knowledge exists for the reactions occurring within an organism” (specification page 4, first paragraph). Thus, one skilled in the art would have had no reasonable expectation of successfully achieving Applicant’s claimed methods.

In light of the teaching away in Pramanik et al. and the lack of motivation to combine the teaching of Pramanik et al. with that of Blattner et al., Applicant maintains that the invention as claimed is unobvious over the cited art. Therefore, withdrawal of this ground of rejection is respectfully requested.

Claim 64 stands rejected under 35 U.S.C. § 103 as allegedly obvious over Pramanik et al., *supra*, in view of Blattner et al., *supra*, and further in view of Xie et al., *TIBTECH* 15:109-113 (1997). As discussed above, neither of Pramanik et al., alone or in combination with Blattner et al., teaches or suggests Applicant’s claimed methods. Moreover, Xie et al. fails to cure the deficiencies of these references. At best, Xie et al. describes the design of media and feeding strategies for fed-batch cultures of animal cells. However, Xie et al. provides no teaching or suggestion, alone or when combined with Pramanik et al. and/or Blattner et al., of the claimed methods. Accordingly, Applicant submits that the invention as claimed is unobvious over the cited art. Therefore, withdrawal of this ground of rejection is respectfully requested.

In light of the amendments and remarks herein, Applicant submits that the claims are now in condition for allowance and respectfully requests a notice to this effect. The Examiner is invited to call the undersigned if there are any questions.

To the extent necessary, a petition for an extension of time under 37 C.F.R. 1.136 is hereby made. Please charge any shortage in fees due in connection with the filing of this paper, including extension of time fees, to Deposit Account 502624 and please credit any excess fees to such deposit account.

Respectfully submitted,

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